Tetrahedron Vol. 49, No. 12, pp. 2413-2426, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

New Total Synthesis of (+)-*N*-Methylanisomycin by Anodic Cyclization of δ-Alkenylamine

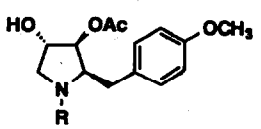
Masao Tokuda,* Hirotake Fujita, Tohru Miyamoto, and Hiroshi Suginome*

Organic Synthesis Division, Department of Chemical Process Engineering, Faculty of Engineering, Hokkaido University, Sapporo 060, Japan

(*Received in Japan* 20 *November* 1992)

Abstract: A chiral total synthesis of (+)-*N*-methylanisomycin (**1a**) from L-diethyl tartrate *via* 15 steps is reported. The key step in the synthesis was a regio- and stereoselective cyclization of (*E*)-δ-alkenylamine **12a** or its (*Z*)-isomer **12b** by anodic oxidation of their lithium amides to give a substituted pyrrolidine **20**. Thus, a Wittig reaction of 4-*O*-acetyl-2,3-*O*-bis(methoxymethyl)-L-threose (**15**), derived from L-diethyl tartrate *via* 6 steps, with 4-methoxyphenylmethylene-triphenylphosphorane gave (*E*)- and (*Z*)-(3*S*,4*S*)-5-acetoxy-3,4-bis[(methoxymethyl)oxy]-1-(4-methoxyphenyl)pent-1-ene (**16a** and **16b**) in 78% yield. Hydrolysis of the acetate **16a** or **16b** followed by a Swern oxidation gave the corresponding substituted 5-(4-methoxyphenyl)pent-4-enal **17a** or **17b** in 93% yield. A reductive amination of the aldehyde **17a** or **17b** with methylamine gave (*E*)- or (*Z*)-(2*S*,3*S*)-*N*-methyl-2,3-bis[(methoxymethyl)oxy]-5-(4-methoxyphenyl)pent-4-enylamine (**12a** or **12b**) in 88% yield. The anodic cyclization of δ-alkenylamine **12a** or **12b** gave (2*R*,3*S*,4*S*)-2-(4-methoxybenzyl)-3,4-*O*-bis(methoxymethyl)-1-methylpyrrolidine (**20**) in 53% yield. Selective protection of the sterically less hindered 4-hydroxyl group of vicinal diol **21** followed by acetylation of the resulting monoalcohol **22** and a final deprotection of the 4-hydroxyl group of the acetate **23** gave (+)-*N*-methylanisomycin.

The antibiotic (-)-anisomycin (**1b**),[1,2] which exhibited selective and potent action against pathogenic protozoa and certain strains of fungi,[3] was originally isolated from culture filtrates of *Streptomyces*.[4] It has been used clinically for the treatment of tricomonas vaginitis and amebic dysentry.[5] The total synthesis of (±)-anisomycin[6] and a number of chiral syntheses of (-)-[7] and (+)-anisomycin[7h,8] have been reported by several groups of workers using different approachs. Thus, in these syntheses, the formation of the pyrrolidine ring has been achieved by an intramolecular nucleophilic displacement of appropriate functions with amine nitrogen,[7c-7e,7g-7i] by an intramolecular nucleophilic addition of amine nitrogen to the carbonyl group,[7a,7b,7f] by an amidomercuration of unsaturated amide,[7j] or by a Dieckmann cyclization of aminodiester.[6a]



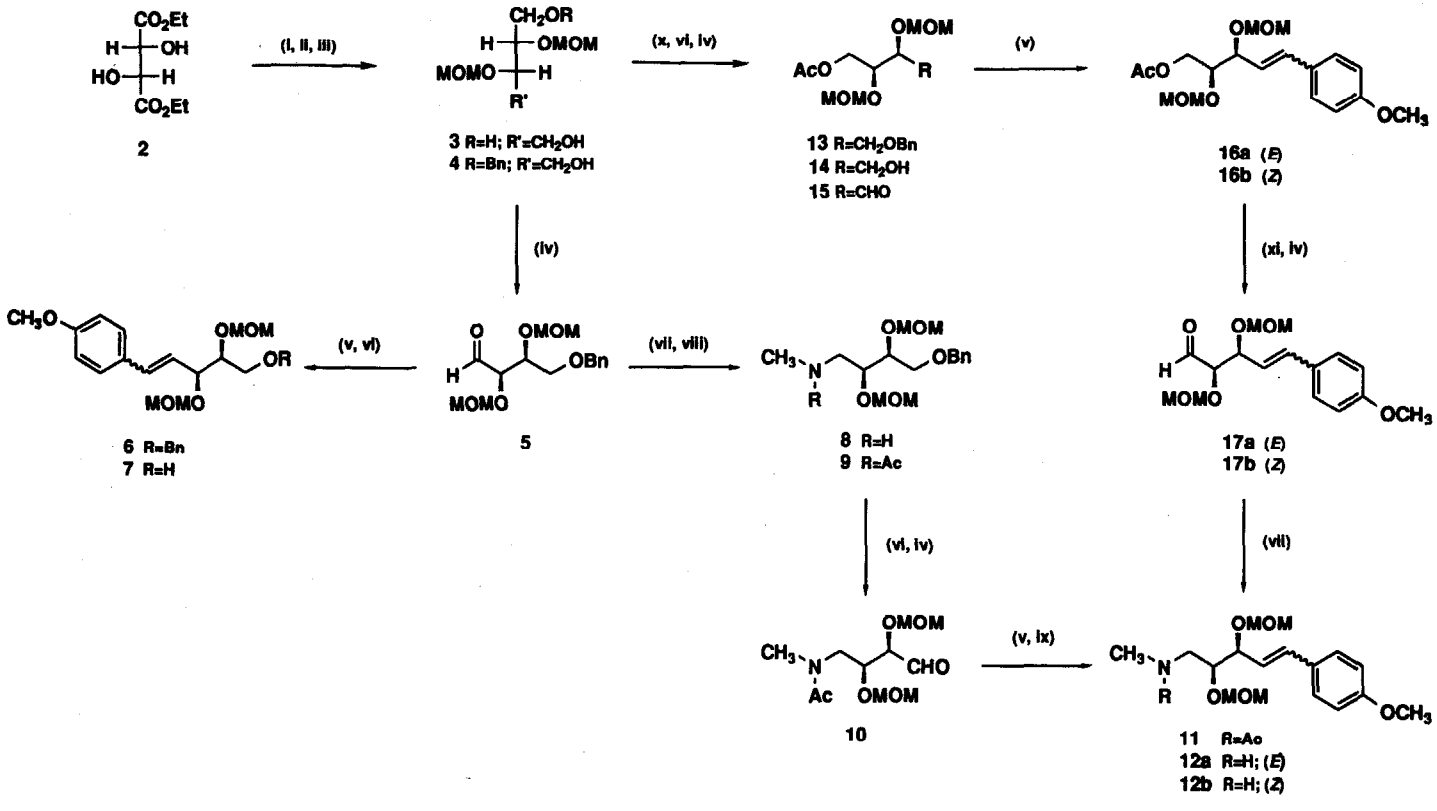
1a R=CH_3
1b R=H

We previously reported that pyrrolidine rings can be obtained by anodic oxidation of lithium δ-alkenylamides generated from δ-alkenylamines.[9] These cyclizations took place in a regio- and stereoselective manner to give *cis*-1-methyl-2,5-disubstituted pyrrolidines in up to 52% yields.[9] The anodic cyclization of δ-alkenylamines carrying a phenyl group at the terminal carbon of their double bonds gave higher yields of 4- or 5-substituted 2-benzyl-1-methylpyrrolidines (66-85% yields).[10] As one of the synthetic applications of these anodic cyclizations we carried out a total synthesis of (+)-*N*-methylanisomycin (**1a**). *N*-Methylanisomycin is expected to possess some pharmacological activity like codonopsine or codonopsinine isomers.[11] We report here on a new chiral synthesis of (+)-*N*-methylanisomycin (**1a**) by the anodic cyclization of δ-alkenylamine as a key step. The synthesis required 15 steps, including 9 steps of protection and deprotection of the functional groups, and an overall isolated yield of this synthesis was 14%.

PREPARATION OF δ-ALKENYLAMINE 12a AND 12b FOR THE ANODIC CYCLIZATION

The δ-alkenylamine **12** required for the synthesis of **1a** was prepared after several unsuccessful attempts. 4-*O*-Benzyl-2,3-*O*-bis-(methoxymethyl)-L-threose (**5**), a chiral building block, was prepared according to a modified method reported by Kibayashi and colleagues,[7e] as outlined in Scheme 1 . Thus, the methoxymethylation of L-diethyl tartrate (**2**) with dimethoxymethane, followed by reduction with $LiAlH_4$, gave diol **3** in 94% yield. Monobenzylation of the diol **3** with 1 equiv. of benzyl bromide in the presence of a phase-transfer catalyst gave monobenzyl ether **4** in 85% yield. A Swern oxidation of **4** gave an aldehyde **5** in quantitative yield. A Wittig reaction of **5** with 4-methoxyphenylmethylenetriphenylphosphorane afforded a 60:40 mixture of (*E*)- and (*Z*)-olefins **6** in 25% yield.[12] Hydrogenolysis of benzyl ether **6** over Pd/C, however, resulted in hydrogenation of the carbon-carbon double bond in preference to removing the benzyl group to give the desired alcohol **7**. A reductive amination[10,13] of aldehyde **5** with methylamine in the presence of sodium cyanoborohydride gave *N*-methylamine **8** in 83% yield. Acetylation of amine **8** and removal of the benzyl group of the resulting *N*-acetate **9** by hydrogenolysis over Pd/C, followed by a Swern oxidation of the resulting alcohol, gave an aldehyde **10** in 87% yield. A Wittig reaction of **10** with 4-methoxyphenylmethylenetriphenylphosphorane gave olefin **11** in 36% yield (*E*:Z=67:33).[12] Deacetylation of **11** with a base under various conditions (5% KOH/MeOH, conc NH_3/MeOH, or MeLi/THF), however, failed to give an acceptable yield of methylamine **12**.

N-Methylalkenylamines **12a** and **12b** were finally obtained by the following sequence of the reactions. Acetylation of monobenzyl ether **4** followed by removing the benzyl group by hydrogenolysis over Pd/C gave the corresponding alcohol **14** in 92% yield. The yield of alcohol **14** from **2** could be increased up to 96.5% by carrying out each step without purifying the intermediary products. A Swern oxidation of alcohol **14** gave the corresponding aldehyde **15**. A Wittig reaction of **15** with 4-methoxyphenylmethylenetriphenylphosphorane gave a 80:20 mixture of (*E*)- (**16a**) and (*Z*)-alkenes (**16b**) in 78% yield from **14**. The Wittig reaction of **15** under various conditions indicated that highest yield of **16** can be attained when aldehyde **15** is subjected to the reaction with 2.5 equiv. of (4-methoxybenzyl)triphenylphosphonium bromide in the presence of 2.5 equiv. of sodium hydride in THF at room temperature for 10 h. The separation of (*E*)- and (*Z*)-isomers by column chromatography gave pure (*E*)-isomer (**16a**) and a 77:23 mixture of (*Z*)- (**16b**) and (*E*)-isomers (**16a**). The (*E*)- and (*Z*)-isomers were successfully separated at the stage of the alcohols obtained by the hydrolysis of **16a** and **16b**. The hydrolysis of the mixture of **16a** and **16b** with KOH in methanol gave a mixture of isomeric alcohols (**7**), the



Scheme 1

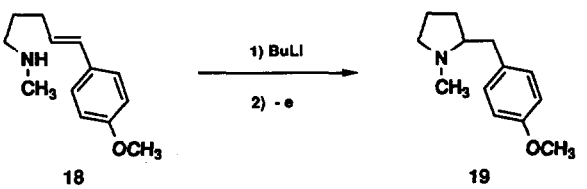
(i) $CH_2(OCH_3)_2$, cat. P_2O_5; (ii) $LiAlH_4$; (iii) BnBr, 4N NaOH, cat. Bu_4NBr; (iv) $(COCl)_2$, Et_3N, DMSO; (v) p-$MeOC_6H_4CH{=}PPh_3$; (vi) H_2; Pd/C;

(vii) CH_3NH_2·HCl, $Na(CN)BH_3$; (viii) Ac_2O, Et_3N; (ix) 5% KOH, MeOH or conc NH_3, MeOH or MeLi, THF; (x) Ac_2O, Et_3N; (xi) KOH, MeOH

recrystallization of which gave a pure crystalline (*E*)-alcohol and an oily (*Z*)-alcohol containing 18% of (*E*)-alcohol. Removal of the acetyl group from **16a** followed by Swern oxidation gave (*E*)-γ-alkenal (**17a**) in 93% yield. Reductive amination[13] of **17a** with methylamine then gave (*E*)-δ-alkenylamine **12a** for anodic cyclization in 88% yield. (*Z*)-Isomer **12b** was similarly obtained from (*Z*)-isomer **16b**. The overall isolated yield of **12** from L-diethyl tartrate was 62%.

SYNTHESIS OF (+)-*N*-METHYLANISOMYCIN BY ANODIC CYCLIZATION OF δ-ALKENYLAMINES 12a AND 12b

We have already reported that the anodic oxidation of lithium amide of *N*-methyl-5-phenylpent-4-enylamine gave 2-benzyl-1-methylpyrrolidine in 70% yield.[10] We have now found that *N*-methyl-5-(4-methoxyphenyl)-pent-4-enylamine (**18**), as a model compound, similarly gives the corresponding pyrrolidine **19** by anodic oxidation (Scheme 2). Thus, the treatment of **18** with butyllithium at -78 °C followed by anodic oxidation of the resulting lithium amide of **18** with a platinum anode and cathode (divided cell) at a constant current of 17.5 mA/cm^2 in a 100:1 mixture of THF and HMPA containing 0.25M lithium perchlorate at -10 °C gave the pyrrolidine **19** in 39% yield.



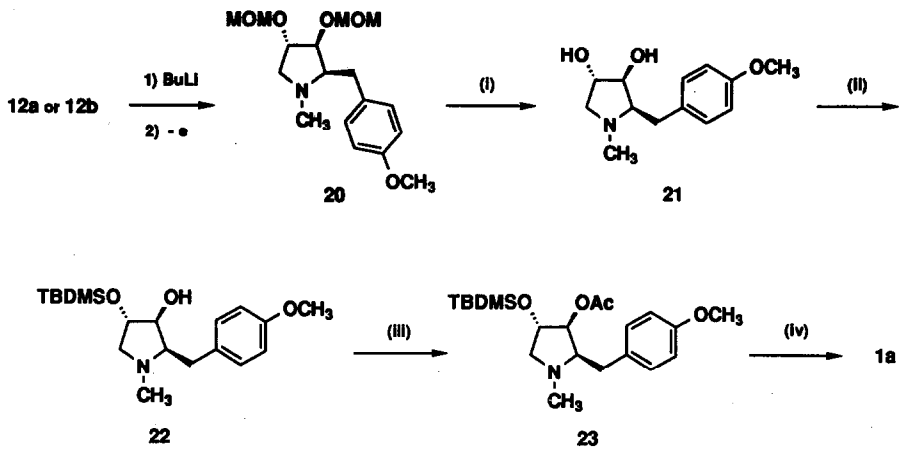
18 **19**

Scheme 2

The treatment of (*E*)-δ-alkenylamine **12a** with butyllithium at -78 °C, followed by anodic oxidation of the resulting lithium amide under the same conditions as those of **18**, gave the pyrrolidine **20** as a single stereoisomer in 53% yield (Scheme 3). The observed high stereoselectivity giving **20** in this electrochemical cyclization might be attributable to the absorption of the radical species on their unhindered face by the electrode surface.[14] A similar anodic oxidation of the lithium amide of (*Z*)-isomer **12b** also gave the pyrrolidine **20**, which was identical to that obtained from (*E*)-isomer **12a**.

Recently we have reported the new anionic cyclization of δ-alkenylamines catalyzed with butyllithium to give *cis*-2,5-disubstituted pyrrolidines stereoselectively.[15] However, we have confirmed that the present cyclizations of **18** and **12a** to afford **19** and **20**,respectively, could not occur in the presence of butyllithium alone.

The ^{1}H NMR spectrum of **20** indicated a multiplet signal at δ2.43, a double-doublet signal at δ2.56, and three doublet signals at δ3.09, 3.84, and 3.98, which are assignable to the 2α, 5β, 5α, 4β, and 3α protons, respectively. The coupling constants between the 2α, 3α protons and the 4β, 5β protons are 4.4 and 4.9 Hz, respectively, while virtually no couplings between the 3α, 4β protons and the 4β, 5α protons were observed. When the signal at δ2.43 due to the 2α proton was irradiated, an NOE enhancement was observed in the signal at δ3.98 due to the 3α proton. These results indicated that the protons attached to the 2 and 3 positions of



Scheme 3

(i) conc. HCl, wet MeOH; (ii) TBDMSCl, Imidazole, DMF; (iii) Ac_2O, Et_3N; (iv) Bu_4NF, THF

pyrrolidine **20** are *cis* oriented. The stereochemistry assigned for pyrrolidine **20** was further confirmed by an analysis of ^1H NMR spectrum of 3-acetoxy-2-(4-methoxybenzyl)-1-methyl-4-[(*tert*-butyldimethylsilyl)oxy]-pyrrolidine (**23**), obtained as described below. An NOE enhancement was also observed between the signals of the 2α, 3α protons and the 4β, 5β protons. Details concerning the analysis results are described in the Experimental.

Removal of the methoxymethyl groups of **20** with hydrochloric acid in methanol gave vicinal diol **21** in 82% yield. The treatment of **21** with *tert*-butyldimethylsilyl chloride and imidazole according to a procedure by Kibayashi[7e] gave, selectively, monosilyl ether **22** in 85% yield. Acetylation of the 3β-hydroxy group of **22** with acetic anhydride and triethylamine, followed by a treatment of the resulting acetate **23** with tetrabutylammonium fluoride in THF, gave (+)-*N*-methylanisomycin (**1a**) in 77% yield.

EXPERIMENTAL

The ^1H NMR spectra were measured in $CDCl_3$ with a JEOL EX-400 spectrometer (400 MHz), using tetramethylsilane as an internal standard. The IR spectra were measured with a JASCO IR-810 spectrometer. The mass spectra were measured with a JEOL JMS-D300 mass spectrometer. Optical rotations were measured in a 10 mm-microcell with a JASCO DIP-360. Merck silica gel 60 PF_{254} and Merck silica gel 60 were used for TLC and column chromatography, respectively.

5-Benzyloxy-3,4-bis[(methoxymethyl)oxy]-1-(4-methoxyphenyl)pent-1-ene (6). To a stirred suspension of (4-methoxybenzyl)triphenylphosphonium bromide (0.19 g, 0.4 mmol) in dry THF (6 mL) was added butyllithium (1.6 M solution in hexane, 0.48 mmol) at 0 °C; the mixture was stirred for 30 min. A solution

of 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threose **5**[7e] (0.13 g, 0.48 mmol) in dry THF (4 mL) was added dropwise to the solution of the ylide; the solution was stirred at room temperature for 2 h. After the reaction mixture was dissolved in diethyl ether (50 mL), the solution was quenched with H_2O (10 mL). The organic phase was washed with H_2O (5 mLx3) and saturated NaCl (5 mL), and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by TLC ($CHCl_3$/hexane=9/1) gave **6** (48.4 mg, 25 %)[12]: IR (neat) 1648, 1607, 1511, 1030, 918, 738, 698 cm^{-1}; ^1H NMR δ3.37 and 3.39 (each s, 6H, (*Z*)), 3.38 and 3.40 (each s, 6H, (*E*)), 3.77 (s, 3H, (*Z*)), 3.80 (s, 3H, (*E*)), 3.6-4.0 (m, 3H), 4.4-4.9 (m, 7H), 5.59 (dd, 1H, (Z)), 6.01 (dd, 1H, *J*=7.7, 16.1 Hz, (*E*)), 6.58 (d, 1H, *J*=16.1 Hz, (*E*)), 6.79 (d, 1H, *J*=9.2 Hz, (Z)), 6.85 (d, 2H, *J*=8.8 Hz), 7.31 (m, 7H); FDMS *m/z* (rel intensity) 402 (100).

***N*-Acetyl-*N*-methyl-4-benzyloxy-3,4-bis[(methoxymethyl)oxy]butylamine (9).** To a solution of methylamine hydrochloride (0.27 g, 4 mmol) in MeOH (6 mL) was added 4-*O*-benzyl-2,3-*O*-bis-(methoxymethyl)-L-threose (**5**)[7e] (0.23 g, 0.8 mmol) in MeOH (4 mL) and then sodium cyanoborohydride (83 mg, 1.3 mmol). The mixture was stirred overnight at room temperature. After evaporation of the solvent, the residue was dissolved in diethyl ether (50 mL) and the ethereal solution was treated with 5% NaOH (5 mL). The organic phase was separated and the aqueous solution was extracted with diethyl ether (5 mL x3). The combined extracts were dried over Na_2SO_4. Filtration and evaporation of the solvent gave *N*-methyl-4-benzyloxy-3,4-bis[(methoxymethyl)oxy]butylamine (**8**) (0.21 g, 84%).

To dry triethylamine (10 mL) was added **8** (0.19 g, 0.6 mmol) and acetic anhydride (1 mL, 10 mmol); the mixture was then stirred for 8 h at room temperature. After evaporation of triethylamine and acetic anhydride, the residue was dissolved in diethyl ether (50 mL). The ethereal solution was washed with H_2O (5 mLx3) and saturated NaCl (5 mL), and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by TLC ($CHCl_3$/hexane=2/1) gave **9** (95 mg, 58%): IR (neat) 3452, 1647, 1028, 918, 742, 700 cm^{-1}; ^1H NMR δ2.07 and 2.13 (each s, 3H), 2.94 and 3.07 (each s, 3H), 3.31 and 3.34 (each s, 3H), 3.40 (s, 3H), 3.55-3.72 (m, 4H), 3.82 (m, 1H), 3.95-4.15 (m, 1H), 4.53-4.82 (m, 6H), 7.33 (m, 5H); MS *m/z* (rel intensity) 356 (M^++1, 0.6), 355 (M^+, 0.4), 207 (21), 172 (24), 160 (51), 99 (29), 91 (100), 86 (79), 45 (94). HRMS calcd for $C_{18}H_{29}NO_6$: *m/z* 355.1995. Found: *m/z* 355.1980.

Compounds 10 and 11. Hydrogenolysis of **9** (0.5 g, 1.4 mmol) over 10% Pd/C followed by Swern oxidation gave 4-(*N*-acetyl-*N*-methyl)amino-2,3-bis[(methoxymethyl)oxy]butanal (**10**) (0.17 g, 47%).

A Wittig reaction of **10** (0.17 g, 0.65 mmol) with 4-methoxyphenylmethylenetriphenylphosphorane (0.6 mmol) gave **11** (*E*:*Z*=67:33) in 36% yield.[12] Hydrolysis of **11** with 5% KOH/MeOH gave **12a** and **12b** in 30% yield. The preparation of **12** through intermediates **5**, **8**, **9**, **10** and**11** was not carried out further because of the poor yield of **12**.

1-*O*-Acetyl-4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threitol (13). A mixture of 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-L-threitol (**4**)[7e] (18.2 g, 61 mmol), dry triethylamine (100 mL), and acetic anhydride (10 mL) was stirred at room temperature for 8 h. After triethylamine and acetic anhydride were evaporated, the residue was dissolved in diethyl ether (200 mL). The ethereal solution was washed with water (10 mLx3) and a saturated NaCl solution, and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by column chromatography (hexane/EtOAc= 4/1) gave **13** (20.3 g, 98%) as an oil: $[\alpha]^{24}_D$ -14.3° (c=1.0, MeOH); IR (neat) 1744, 1238, 1106, 1029, 918 cm^{-1}; ^1H NMR δ2.06 (s, 3H), 3.38 (s, 6H), 3.61 (dd, 1H, *J*=5.6, 10.0

Hz), 3.68 (dd, 1H, *J*=5.0, 10.0 Hz), 3.92 (m, 1H), 4.01 (m, 1H), 4.18 (dd, 1H, *J*=6.2, 11.5 Hz), 4.31 (dd, 1H, *J*=4.6, 11.5 Hz), 4.54 (s, 2H), 4.69 (d, 2H, *J*=7.1 Hz), 4.72 (d, 1H, *J*=6.8 Hz), 4.79 (d, 1H, *J*=6.8 Hz); FDMS *m/z* (rel intensity) 341 (M^+, 55), 297 (100), 147 (8), 91 (7).

1-*O*-Acetyl-2,3-*O*-bis(methoxymethyl)-L-threitol (14). Threitol **13** (20 g, 581 mmol) was hydrogenated over 5% Pd/C (10 g) at 1 atm of hydrogen in ethyl acetate (500 mL) for 1 h. Filtration over Celite and then evaporation of the solvent gave **14** (13.8 g, 94%): $[\alpha]^{24}_D$ -22.9° (c=1.0, MeOH); IR (neat) 3468, 1741, 1241, 1021, 918 cm^{-1}; ^1H NMR δ2.08 (s, 3H), 3.01 (bs, 1H), 3.42 (s, 3H), 3.44 (s, 3H), 3.7-3.8 (m, 3H), 3.98 (m, 1H), 4.18 (dd, 1H, *J*=6.6, 11.6 Hz), 4.31 (d, 1H, *J*=4.6, 11.6 Hz), 4.69 (d, 1H, *J*=6.8 Hz), 4.70 (d, 1H, *J*=6.8 Hz), 4.75 (d, 1H, *J*=6.8 Hz), 4.77 (d, 1H, *J*=6.8 Hz); FDMS *m/z* (rel intensity) 253 (M^+, 100), 221 (37), 177 (15), 147 (20), 103 (17), 45 (76).

4-*O*-Acetyl-2,3-*O*-bis(methoxymethyl)-L-threose (15). To a stirred and cooled (-78 °C) solution of oxalyl chloride (10.2 g, 80 mmol) in CH_2Cl_2 (140 mL) was added dropwise a solution of DMSO (12.5 g, 160 mmol) in CH_2Cl_2 (10 mL); the mixture was stirred at -78 °C for 15 min. To this mixture was added dropwise a solution of **14** (10.1 g, 40 mmol) in CH_2Cl_2 (50 mL). After 1 h of stirring at -78 °C, triethylamine (48.5 g, 240 mmol) was added and the reaction mixture was stirred for an additional 15 min. The mixture was then allowed to warm to room temperature before adding 10% aqueous sodium acetate (40 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mLx3); the combined extracts were dried over Na_2SO_4. Filtration followed by evaporation of the solvent gave pure **15** (9.9 g, 100%): $[\alpha]^{24}_D$ -2.0° (c=1.0, MeOH); IR (neat) 1742, 1240, 1031, 919 cm^{-1}; ^1H NMR δ2.08 (s, 3H), 3.36 (s, 3H), 3.44 (s, 3H), 4.15 (dd, 1H, *J*=1.0, 3.4 Hz), 4.24 (m, 1H), 4.29 (m, 2H), 4.65 (d, 1H, *J*=6.8 Hz), 4.73 (d, 1H, *J*=6.8 Hz), 4.75 (d, 1H, *J*=6.8 Hz), 4.82 (d, 1H, *J*=6.8 Hz), 9.77 (d, 1H, *J*=1.0 Hz); FDMS *m/z* (rel intensity) 251 (M^+, 100), 221 (88), 147 (23), 103 (22), 45 (84).

(*E*)-(3*S*,4*S*)-5-Acetoxy-3,4-bis[(methoxymethyl)oxy]-1-(4-methoxyphenyl)pent-1-ene (16a). To a stirred suspension of (4-methoxybenzyl)triphenylphosphonium bromide (55.1 g, 0.12 mol) in dry THF (400 mL) was added sodium hydride (4.76 g, 0.12 mol); the mixture was then stirred overnight at room temperature. After a solution of **15** (9.9 g, 40 mmol) in dry THF (100 mL) was added dropwise to a solution of the ylide; it was stirred at room temperature for 2 h. The reaction mixture was dissolved in diethyl ether (500 mL), and then quenched with a saturated solution of NH_4Cl at 0 °C. The organic phase was washed with water (20 mLx3) and saturated NaCl solution (20 mL), and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by column chromatography (diethyl ether) gave a 82:18 mixture of (*E*)- (**16a**) and (*Z*)- (3*S*, 4*S*)-5-acetoxy-3,4-bis[(methoxymethyl)oxy]-1-(4-methoxyphenyl)pent-1-ene (**16b**) (11.0 g, 78%). Further separation by column chromatography (hexane/EtOAc=10/1) gave pure **16a**: IR (neat) 1742, 1653, 1608, 1514, 1253, 1030, 976, 919 cm^{-1}; ^1H NMR δ2.07 (s, 3H), 3.39 (s, 3H), 3.41 (s, 3H), 3.82 (s, 3H), 3.93 (m, 1H), 4.17 (dd, 1H, *J*=6.4, 11.7 Hz), 4.35 (dd, 1H, *J*=4.4, 11.7 Hz), 4.36 (dd, 1H, *J*=4.4, 7.6 Hz), 4.60 (d, 1H, *J*=6.8 Hz), 4.77 (d, 1H, *J*=6.8 Hz), 4.78 (s, 2H), 6.00 (dd, 1H, *J*=7.6, 15.6 Hz), 6.59 (d, 1H, *J*=15.6 Hz), 6.85 (d, 2H, *J*=8.8Hz), 7.32 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel internsity) 354 (M^+, 1), 207 (64), 147 (25), 45 (100). HRMS calcd for $C_{18}H_{26}O_7$: *m/z* 354.1678. Found: *m/z* 354.1699.

(*Z*)-(3*S*,4*S*)-5-Acetoxy-3,4-bis[(methoxymethyl)oxy]-1-(4-methoxyphenyl)pent-1-ene (16b). Separation of **16a** and **16b** by column chromatography (hexane/EtOAc=10/1) gave 70% pure **16b**: IR (neat) 1743, 1638, 1609, 1513, 1252, 1030, 919 cm^{-1}; ^1H NMR δ1.93 (s, 3H), 3.34 (s, 3H), 3.39 (s, 3H), 3.81 (s, 3H), 3.93 (m, 1H), 4.18 (dd, 1H, *J*=5.6, 11.5 Hz), 4.30 (dd, 1H, *J*=4.6, 11.5 Hz), 4.58 (d, 1H, *J*=6.8 Hz), 4.71 (d, 1H, *J*=6.8 Hz), 4.74 (d, 1H, *J*=6.8 Hz), 4.75 (d, 1H, *J*=6.8 Hz), 4.87 (dd, 1H, *J*=4.9, 10.2 Hz), 5.53 (dd, 1H, *J*=10.2, 12.0 Hz), 6.68 (d, 1H, *J*=12.0 Hz), 6.86 (d, 2H, *J*=8.8 Hz), 7.27 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 354 (M^+, 0.7), 207 (61), 147 (30), 45 (100). HRMS calcd for $C_{18}H_{26}O_7$: *m/z* 354.1678. Found: *m/z* 354.1665.

(2*S*,3*S*)-2,3-Bis[(methoxymethyl)oxy]-5-(4-methoxyphenyl)pent-4-enal (17a and 17b). To a solution of **16a** (2.0 g, 5.6 mmol) in MeOH (20 mL) was added 10% KOH/MeOH (60 mL); the mixture was then stirred at room temperature for 1 h. After evaporation of the solvent, the residue was dissolved in diethyl ether (100 mL). The ethereal solution was washed with H_2O (5 mLx3) and saturated NaCl (5 mLx3), and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by recrystallization from hexane/$CHCl_3$ gave (*E*)-(2*S*,3*S*)-2,3-bis[(methoxymethyl)oxy]-5-(4-methoxyphenyl)pent-4-enol ((*E*)-**7**): mp 77.8-78.6 °C; $[\alpha]^{24}_D$ +63.8° (c=1.0, MeOH); IR (Nujol) 3358, 3272, 1606, 1511, 1244, 1034, 970 cm^{-1}; ^1H NMR δ2.90 (bs, 1H), 3.41 (s, 3H), 3.45 (s, 3H), 3.7-3.8 (m, 3H), 3.81 (s, 3H), 4.35 (dd, 1H, *J*=4.4, 7.8 Hz), 4.59 (d, 1H, *J*=6.4 Hz), 4.76 (d, 1H, *J*=6.4 Hz), 4.77 (d, 1H, *J*=6.8 Hz), 4.82 (d, 1H, *J*=6.8 Hz), 6.00 (dd, 1H, *J*=7.8, 15.6 Hz), 6.58 (d, 1H, *J*=15.6 Hz), 6.86 (d, 2H, *J*=8.8 Hz), 7.33 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 312 (M^+, 1.5), 207 (65), 147 (24), 45 (100). HRMS calcd for $C_{16}H_{24}O_6$: *m/z* 312.1573. Found: *m/z* 312.1547.

Evaporation of the solvent from the mother liquor obtained in the recrystallization of the (*E*)-pent-4-enol gave (*Z*)-(2*S*,3*S*)-2,3-bis[(methoxymethyl)oxy]-5-(4-methoxyphenyl)pent-4-enol ((*Z*)-**7**) as an oil (*Z*:*E*=71: 29): IR (neat) 3462, 1608, 1513, 1252, 1030, 918 cm^{-1}; ^1H NMR δ2.92 (bs, 1H), 3.32 (s, 3H), 3.44 (s, 3H), 3.7-3.8 (m, 3H), 3.81 (s, 3H), 4.55 (d, 1H, *J*= 6.8 Hz), 4.63 (d, 1H, *J*=6.8 Hz), 4.75 (d, 1H, *J*=6.8 Hz), 4.79 (d, 1H, *J*= 6.8 Hz), 4.77-4.83 (m, 1H), 5.56 (dd, 1H, *J*=10.2, 12.2 Hz), 6.69 (d, 1H, *J*= 12.2 Hz), 6.87 (d, 2H, *J*=8.8 Hz), 7.24 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 312 (M^+, 0.1), 207 (46), 147 (24), 45 (100). HRMS calcd for $C_{16}H_{24}O_6$: *m/z* 312.1573. Found: *m/z* 312.1548.

A solution of DMSO (1.0 g, 12.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred and cooled (-78 °C) solution of oxalyl chloride (0.81 g, 6.4 mmol) in CH_2Cl_2 (40 mL); the mixture was then stirred at -78 °C for an additional 15 min. To the reaction mixture was added dropwise a solution of (*E*)-alkenol **7** (1.0 g, 3.2 mmol) in CH_2Cl_2 (20 mL) at -78 °C; the mixture was stirred for 1 h. Triethylamine (1.94 g, 19.2 mmol) was added to the reaction mixture at -78 °C and it was stirred for 15 min. After the mixture was allowed to warm to room temperature, 10% aqueous sodium acetate (10 mL) was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (5 mLx3); the combined extracts were then dried over Na_2SO_4. Filtration and evaporation of the solvent gave pure (*E*)-(2*S*,3*S*)-2,3-bis[(methoxymethyl)oxy]-5-(4-methoxyphenyl)pent-4-enal (**17a**) (993 mg, 100%): IR (neat) 1734, 1677, 1608, 1513, 1252, 1026, 919 cm^{-1}; ^1H NMR δ3.33 (s, 3H), 3.44 (s, 3H), 3.81 (s, 3H), 4.07 (dd, 1H, *J*=1.5, 2.9 Hz), 4.54 (d, 1H, *J*=6.8 Hz), 4.68 (dd, 1H, *J*= 2.9, 8.3 Hz), 4.76 (d, 1H, *J*=6.8 Hz), 4.78 (d, 1H, *J*=6.8 Hz), 4.84 (d, 1H, *J*= 6.8 Hz), 6.09 (dd, 1H, *J*=8.3, 16.1 Hz), 6.65 (d, 1H, *J*=16.1 Hz), 6.87 (d, 2H, *J*=8.8 Hz), 7.34 (d, 2H, *J*=8.8 Hz), 9.80 (d, 1H,

J=1.5 Hz); MS *m/z* (rel intensity) 310 (M^+, 0.1) 217 (3), 207 (50), 147 (17), 45 (100). HRMS calcd for $C_{16}H_{22}O_6$: *m/z* 310.1416. Found: *m/z* 310.1420.

(*Z*)-Alkenol **7** was oxidized in the same way as that of the (*E*)-isomer, as described above, to give (*Z*)-(2*S*,3*S*)-2,3-bis[(methoxymethyl)oxy]-5-(4-methoxyphenyl)pent-4-enal (**17b**) : IR (neat) 1735, 1682, 1608, 1512, 1254, 1030, 919 cm^{-1}; ^1H NMR δ3.26 (s, 3H), 3.44 (s, 3H), 3.82 (s, 3H), 4.10 (dd, 1H, *J*=1.5, 3.3 Hz), 4.51 (d, 1H, *J*=6.8 Hz), 4.67 (d, 1H, *J*=6.8 Hz), 4.77 (d, 1H, *J*=6.8 Hz), 4.82 (d, 1H, *J*=6.8 Hz), 5.14 (dd, 1H, *J*=3.3, 9.6 Hz), 5.66 (dd, 1H, *J*=9.6, 12.0 Hz), 6.72 (d, 1H, *J*=12.0 Hz), 6.89 (d, 1H, *J*=8.8 Hz), 7.2 (d, 1H, *J*=8.8 Hz), 9.76 (d, 1H, *J*=1.5 Hz); MS *m/z* (rel intensity) 310 (M^+, 0.1), 248 (2), 207 (46), 147 (24), 45 (100). HRMS calcd for $C_{16}H_{22}O_6$: *m/z* 310.1417. Found: *m/z* 310. 1408.

(*E*)-(2*S*,3*S*)-*N*-Methyl-2,3-bis[(methoxymethyl)oxy]-5-(4-methoxyphenyl)pent-4-enylamine (12a). To a saturated solution of methylamine hydrochloride in MeOH (30 mL) was added **17a** (466 mg, 1.5 mmol) under a nitrogen atmosphere. After 1h of stirring, sodium cyanoborohydride (161 mg, 2.5 mmol) was added to the mixture; the solution was stirred overnight at room temperature. After evaporation of the solvent, the residue was dissolved in diethyl ether (50 mL) and the ethereal solution was treated with 4N-NaOH (10 mL). The organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined extracts were condensed and the residual ethereal solution (10 mL) was made acidic (pH <2) with dil HCl at 0 °C. After removing the impurities with diethyl ether (2 mLx3), the aqueous phase was made basic (pH >9) with KOH. The solution was saturated with NaCl and extracted with diethyl ether (5 mLx5); the combined extracts were then dried over Na_2SO_4. Filtration and evaporation of the solvent gave pure **12a** (488 mg, 88%) as a pale yellow oil: $[\alpha]^{24}_D$ +31.0° (c=1.0, MeOH); IR (neat) 3338, 1650, 1609, 1513, 1252, 1032, 918, 788 cm^{-1}; ^1H NMR δ1.68 (bs, 1H), 2.45 (s, 3H), 2.73 (dd, 1H, *J*=7.3, 12.2 Hz), 2.81 (dd, 1H, *J*=4.4, 12.2 Hz), 3.40 (s, 3H), 3.41 (s, 3H), 3.7-3.9 (m, 1H), 3.81 (s, 3H), 4.37 (m, 1H, *J*=4.4, 5.4, 7.3 Hz), 4.60 (d, 1H, *J*=6.8 Hz), 4.76 (d, 1H, *J*=6.8 Hz), 4.78 (d, 1H, *J*=6.8 Hz), 4.81 (d, 1H, *J*=6.8 Hz), 6.00 (dd, 1H, *J*=7.8, 16.1 Hz), 6.58 (d, 1H, *J*=16.1 Hz), 6.86 (d, 2H, *J*=8.8 Hz), 7.33 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 325 (M^+, 12), 280 (8), 220 (19), 207 (37), 175 (22), 161 (20), 147 (33), 45 (100). HRMS calcd for $C_{17}H_{27}NO_5$: *m/z* 325.1889. Found: *m/z* 325.1892.

(*Z*)-(2*S*,3*S*)-*N*-Methyl-2,3-bis[(methoxymethyl)oxy]-5-(4-methoxyphenyl)pent-4-enylamine (12b). Treatment of (*Z*)-pent-4-enal **17b** with methylamine hydrochloride and sodium cyanoborohydride in the same manner as that of **17a** gave **12b**: $[\alpha]^{24}_D$ +14.7° (c=1.0, MeOH); IR (neat) 3340, 1648, 1608, 1512, 1252, 1031, 918, 844, 788 cm^{-1}; ^1H NMR δ1.85 (bs, 1H), 2.43 (s, 3H), 2.40-2.48 (m, 1H), 2.74 (dd, 1H, *J*=7.3, 12.5 Hz), 2.84 (dd, 1H, *J*=4.4, 12.5 Hz), 3.32 (s, 3H), 3.38 (s, 3H), 3.80 (s, 3H), 3.78-3.84 (m, 1H), 4.55 (d, 1H, *J*=6.6 Hz), 4.66 (d, 1H, *J*=6.6 Hz), 4.72 (d, 1H, *J*=6.6 Hz), 4.75 (d, 1H, *J*=6.6 Hz), 5.53 (dd, 1H, *J*=9.9, 12.0 Hz), 6.68 (d, 1H, *J*= 12.0 Hz), 6.87 (d, 2H, *J*=8.8 Hz), 7.28 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 325 (M^+, 5), 280 (6), 220 (15), 207 (32), 175 (20), 161 (17), 147 (31), 45 (100). HRMS calcd for $C_{17}H_{27}NO_5$: *m/z* 325.1889. Found: *m/z* 325.1892.

Preparation of (*E*)-*N*-Methyl-5-(4-methoxyphenyl)pent-4-enylamine (18). To a mixture of 1,4-butanediol (10.8 g, 0.12 mol) and dihydropyran (10.1 g, 0.12 mol) in THF (20 mL)/CH_2Cl_2 (200 mL) was added a catalytic amount of *p*-toluenesulfonic acid (2.28 g, 12 mmol) at -10 °C; the mixture was stirred for 1 h. The mixture was dissolved in diethyl ether (250 mL). The ethereal solution was washed with water (20 mLx3)

and saturated NaCl solution (20 mL), and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by distillation gave 4-(2-tetrahydropyranyl)oxybutan-1-ol (19.0 g, 91%): bp 98-101 °C (0.45 mmHg); IR (neat) 3390, 1024 cm^{-1}; MS *m/z* (rel intensity) 174 (M^+, 0.3), 101 (21), 85 (100), 73 (95). HRMS calcd for $C_9H_{18}O_3$: *m/z* 174.1256. Found: *m/z* 174.1285.

A solution of DMSO (0.55 g, 7.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred and cooled (-78 °C) solution of oxalyl chloride (0.45 g, 3.5 mmol) in CH_2Cl_2 (15 mL); the mixture was then stirred for 15 min. To this mixture was added dropwise a solution of 4-(2-tetrahydropyranyl)oxybutan-1-ol (307 mg, 1.76 mmol) in CH_2Cl_2 (10 mL) at -78 °C; the mixture was stirred for an additional 1 h. After triethylamine (1.07 g, 10.6 mmol) was added to the mixture at -78 °C, it was stirred for 15 min. The mixture was then allowed to warm to room temperature before treating it with a 10% aqueous solution of sodium acetate (10 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (5 mLx3). The combined extracts were dried over Na_2SO_4. Filtration and evaporation of the solvent gave an almost pure 4-(2-tetrahydropyranyl)oxybutanal (303 mg, 100%): IR (neat) 1726, 1034 cm^{-1}; ^1H NMR δ1.4-1.6 (m, 4H), 1.6-1.8 (m, 2H), 1.95 (m, 2H), 2.55 (m, 2H), 3.42 (dt, 1H), 3.50 (m, 1H), 3.78 (dt, 1H), 3.84 (m, 1H), 4.57 (t, 1H, *J*=3.3 Hz), 9.79 (t, 1H, *J*=1.7 Hz); MS *m/z* (rel intensity) 172 (M^+, 0.1), 101 (14), 85 (66), 71 (100), 56 (18), 41 (34). HRMS calcd for $C_9H_{16}O_3$: *m/z* 172.1098. Found: *m/z* 172.1077.

Sodium hydride (3.0 g, 75 mmol) was added to a stirred suspension of (4-methoxybenzyl)triphenylphosphonium bromide (13.9 g, 30 mmol) in THF (200 mL); the mixture was then stirred overnight at room temperature. To this mixture was added dropwise a THF solution (100 mL) of 4-(2-tetrahydropyranyl)oxy-butanal (4.21 g, 30 mmol); the mixture was then stirred for 2 h. The mixture was dissolved in diethyl ether (300 mL) and the ethereal solution was quenched with a saturated NH_4Cl solution (20 mL) at 0 °C. The organic phase was washed with water (20 mLx3) and saturated NaCl solution (20 mL), and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by column chromatography ($CHCl_3$) gave a 71:29 mixture of (*E*)- and (*Z*)-1-*O*-(2-tetrahydropyranyl)-5-(4-methoxyphenyl)pent-4-enol (7.7 g, 93%): IR (neat) 3026, 1654, 1609, 1578, 1510, 1030, 968 cm^{-1}; MS *m/z* (rel intensity) 276 (M^+, 1.5), 174 (31), 147 (25), 85 (100). 1-*O*-(2-Tetra-hydropyranyl)-5-(4-methoxyphenyl)pent-4-enol (9.1 g, 15.2 mmol) was treated with *p*-toluenesulfonic acid (285 mg, 1.5 mmol) in MeOH (100 mL); the mixture was then stirred at room temperature for 30 min. After evaporation of the solvent, the residue was diluted with diethyl ether (200 mL) and water (20 mL). The mixture was washed with 5% $NaHCO_3$ solution, water (10 mLx3), and a saturated NaCl solution and then dried over Na_2SO_4. Filtration and evaporation of the solvent gave a crude mixture of (*E*)- and (*Z*)-5-(4-methoxyphenyl)-pent-4-en-1-ol (4.8 g, 90%). Recrystallization from hexane/CH_2Cl_2 gave (*E*)-5-(4-methoxyphenyl)pent-4-en-1-ol (2.9 g, 61%): mp 73.3-75.1 °C; IR (Nujol) 3280, 1605, 1574, 1509, 1243, 1028, 969 cm^{-1}; ^1H NMR δ1.46 (bs, 1H), 1.74 (m, 2H), 2.28 (q, 2H), 3.79 (t, 2H), 3.79 (s, 3H), 6.08 (dt, 1H, *J*=6.8, 15.6 Hz), 6.36 (d, 1H, *J*=15.6 Hz), 6.83 (d, 2H, *J*=8.8 Hz), 7.27 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 192 (M^+, 77), 147 (95), 121 (100), 115 (25), 91 (37). HRMS calcd for $C_{12}H_{16}O_6$: *m/z* 192.1151. Found: *m/z* 192.1138.

A solution of DMSO (1.63 g, 20.8 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred and cooled (-78 °C) solution of oxalyl chloride (1.32 g, 10.4 mmol) in CH_2Cl_2 (25 mL); the mixture was then stirred for 15 min at -78 °C. To this mixture was added dropwise a solution of (*E*)-5-(4-methoxyphenyl)pent-4-en-1-ol (1.0 g, 5.2 mmol) in CH_2Cl_2 (15 mL) at -78 °C; the mixture was stirred for 1 h. After triethylamine (3.16 g, 31.2 mmol) was added to the reaction mixture at -78 °C, it was stirred for 15 min. The mixture was then allowed to warm to room temperature before adding a 10% aqueous solution of sodium acetate (10 mL). The organic phase

was separated and the aqueous phase was extracted with CH_2Cl_2 (5 mLx3). The combined extracts were dried over Na_2SO_4. Filtration and evaporation of the solvent gave (*E*)-5-(4-methoxyphenyl)pent-4-enal (988 mg, 100%): IR (neat) 1723, 1653, 1600, 1511, 1250, 1033, 968, 839 cm^{-1}; ^1H NMR δ2.53 (m, 2H), 2.61 (m, 2H), 3.80 (s, 3H), 6.06 (dt, 1H, *J*=6.8, 15.6 Hz), 6.37 (d, 1H, *J*=15.6 Hz), 6.83 (d, 2H, *J*=8.8 Hz), 7.26 (d, 2H, *J*= 8.8 Hz), 9.82 (t, 1H, *J*=1.5 Hz); MS *m/z* (rel intensity) 190 (M^+, 54), 147 (54), 134 (100), 115 (23), 91 (33). HRMS calcd for $C_{12}H_{14}O$: *m/z* 190.0994. Found: *m/z* 190.0993.

To a solution of methylamine hydrochloride (473 mg, 7.0 mmol) in EtOH (15 mL) was added (*E*)-5-(4-methoxyphenyl)pent-4-enal (266 mg, 1.4 mmol) and then sodium cyanoborohydride (44 mg, 0.7 mmol). The mixture was stirred overnight. After evaporation of the solvent, the residue was dissolved in diethyl ether (50 mL) and the ethereal solution was quenched with 4N-NaOH (10 mL). The organic phase was separated and the aqueous phase was extacted with diethyl ether (3 mLx3). The same treatment of the combined extracts as that in the preparation of **12a** gave (*E*)-*N*-methyl-5-(4-methoxyphenyl)pent-4-enylamine (**18**) (248 mg, 86%): IR (neat) 3318, 1648, 1607, 1501, 1247, 1034, 966, 839 cm^{-1}; ^1H NMR δ1.59 (bs, 1H), 1.66 (m, 2H), 2.23 (q, 2H), 2.44 (s, 3H), 2.62 (t, 2H), 3.79 (s, 3H), 6.07 (dt, 1H, *J*=6.8, 15.6 Hz), 6.34 (d, 1H, *J*=15.6 Hz), 6.83 (d, 2H, *J*=8.8 Hz), 7.27 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 205 (M^+, 22), 174 (11), 159 (10), 84 (13), 70 (53), 57 (12), 44 (100). HRMS calcd for $C_{13}H_{19}NO$: *m/z* 205.1467. Found: *m/z* 205.1467.

Anodic Oxidation of Lithium Amide of 18. The electrochemical cell used in this study was an H-type divided cell. Details concerning the apparatus and the procedure for anodic oxidation have already been reported.[10] To a cooled (-78 °C) solution of **18** (148 mg, 0.72 mmol) in THF (6 mL) was added dropwise BuLi (0.86 mmol in hexane) under a nitrogen atmosphere. After 10 min of stirring at -78 °C, HMPA (0.2 mL) was added to the solution, which was then stirred for an additional 5 min. A solution of the lithium amide of **18** was transferred to an anode chamber containing 0.25 M $LiClO_4$-THF (24 mL; 30 mL as a total volume)/ HMPA (0.1 mL; 0.3 mL as a total volume). The mixture in the anode chamber was electrolyzed at a constant current (17.5 mA/cm^2) at -10 °C under a nitrogen atmosphere. The electricity passed was 1.2 Faradays per mol of **18**. After electrolysis, the anolyte was dissolved in diethyl ether (80 mL). The ethereal solution was washed with water (5 mLx3) and a saturated NaCl solution (5 mL), and dried over Na_2SO_4. Filtration and evaporation of the solvent followed by TLC (CH_2Cl_2/MeOH /NH_4OH=200/10/1) gave 1-methyl-2-(4-methoxyphenyl)pyrrolidine (**19**) (58 mg, 39%, R_f=0.18): IR (neat) 1612, 1583, 1509, 1250, 1037, 820 cm^{-1}; ^1H NMR δ1.53 (m, 1H), 1.63 (m, 1H), 1.74 (m, 2H), 2.20 (m, 2H), 2.29 (m, 1H), 2.41 (dd, 1H, *J*=9.5, 13.2 Hz), 2.39 (s, 3H), 3.00 (dd, 1H, *J*=3.9, 13.2 Hz), 3.12 (m, 1H), 3.79 (s, 3H), 6.82 (d, 2H, *J*=8.8 Hz), 7.11 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 205 (M^+, 0.5), 121 (4), 84 (100); HRMS cacld for $C_{13}H_{19}NO$: *m/z* 205.1467. Found: *m/z* 205.1478.

Anodic Oxidation of Lithium Amide of 12a. The anodic oxidation of **12a** was carried out under the same conditions as those of **18**. Thus, to a cooled (-78 °C) solution of **12a** (100 mg, 0.3 mmol) in THF (6 mL) was added BuLi (0.36 mmol in hexane). After the solution was stirred for 10 min, HMPA (0.2 mL) was added to the solution at -78 °C and the mixture was stirred for an additional 5 min. The resulting solution of the lithium amide of **12a** was transferred to an anode chamber containing 0.25 M $LiClO_4$-THF (24 mL)/ HMPA (0.1 mL) and electrolyzed at a constant current (17.5 mA/cm^2) at -10 °C. The electricity passed was 1.2 Faradays per mol of **12a**. The electrolyzed mixture was worked up as described for that of **18**. The product was subjected to preparative TLC (CH_2Cl_2/MeOH/ NH_4OH= 100/10/1) to give (*2R,3S,4S*)-2-(4-methoxybenzyl)-3,4-*O*-bis-

(methoxymethyl)-1-methylpyrrolidine (**20**) (53 mg, 53%): IR (neat) 1612, 1514, 1247, 1035, 918 cm^{-1}; ^1H NMR δ2.38 (s, 3H, NCH_3), 2.43 (m, 1H, *J*=4.4, 4.9, 8.8 Hz, 2α-H), 2.56 (dd, 1H, *J*=4.9, 10.3 Hz, 5β-H), 2.69 (dd, 1H, *J*=8.8, 13.7 Hz, benzyl CH_2), 3.02 (dd, 1H, *J*=4.9, 13.7 Hz, benzyl CH_2), 3.09 (s, 3H, CH_3 of MOM), 3.09 (d, 1H, *J*=10.3 Hz, 5α-H), 3.37 (s, 3H, CH_3 of MOM), 3.78 (s, 3H, anisyl CH_3), 3.84 (d, 1H, *J*=4.9 Hz, 4β-H), 3.98 (d, 1H, *J*=4.4 Hz, 3α-H; *NOE* enhancement (8.2 %) was observed when a multiplet at δ2.43 was irradiated), 4.23 (d, 1H, *J*=6.8 Hz, CH_2 of MOM), 4.44 (d, 1H, *J*=6.8 Hz, CH_2 of MOM), 4.68 (d, 1H, *J*=6.8 Hz, CH_2 of MOM), 4.70 (d, 1H, *J*=6.8 Hz, CH_2 of MOM), 6.83 (d, 2H, *J*=8.8 Hz, aromatic), 7.18 (d, 1H, *J*=8.8 Hz, aromatic); MS *m/z* (rel intensity) 325 (M^+, 0.1), 204 (100), 121 (33), 110 (31), 82 (35), 45 (69). HRMS calcd for $C_{17}H_{27}NO_5$: *m/z* 325.1889. Found: *m/z* 325.1897.

Anodic Oxidation of Lithium Amide of 12b. δ-Alkenylamine **12b** (100 mg, 0.3 mmol) was converted to the corresponding lithium amide, and then anodically oxidized in the same manner as that of **12a**. The amine **12b** used in this study contained 21% of **12a**. The work-up, as described for that of **12a**, gave **20** (50 mg, 50 %), whose IR, ^1H NMR, and mass spectra were completely identical to those of the pyrrolidine **20** obtained from **12a**.

(2*R*,3*S*,4*S*)-3,4-Dihydroxy-2-(4-methoxybenzyl)-1-methyl-pyrrolidine (21). A solution of **20** (669 mg, 2.0 mmol) in MeOH (15 mL)/conc. HCl (2 mL)/H_2O (7.5 mL) was heated under reflux for 15 min. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (50 mL). The resulting solution was neutralized with a 5% $NaHCO_3$ solution. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (5 mLx3); the combined extracts were then dried over Na_2SO_4. Filtration and then evaporation of the solvent, followed by recrystallization of the product from hexane/$CHCl_3$, gave **21** (475 mg, 82%): mp 153-155 °C; $[\alpha]^{24}_D$ +39.1° (c=1.0, MeOH); IR (Nujol) 3332, 1611, 1512, 1243, 1097, 1036, 995 cm^{-1}; ^1H NMR δ2.7 (bs, 2H), 2.30 (m, 1H, *J*=4.9, 5.4, 8.3 Hz), 2.34 (s, 3H), 2.62 (dd, 1H, *J*=4.9, 10.7 Hz), 2.68 (dd, 1H, *J*=8.3, 13.7 Hz), 2.93 (d, 1H, *J*=10.7 Hz), 2.97 (dd, 1H, *J*=4.9, 13.7 Hz), 3.77 (s, 3H), 3.87 (m, 2H), 6.84 (d, 2H, *J*=8.8 Hz), 7.17 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 237 (M^+, 0.1), 121 (11), 116 (100), 44 (32). HRMS calcd for $C_{13}H_{19}NO_3$: *m/z* 237.1365. Found: *m/z* 237.1363.

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.79; H, 8.17; N, 5.98.

(2*R*,3*S*,4*S*)-3-Hydroxy-2-(4-methoxybenzyl)-1-methyl-4-[(*tert*-butyldimethylsilyl)oxy]-pyrrolidine (22). To a solution of **21** (292 mg, 1.2 mmol) in DMF (10 mL) was added imidazole (196 mg, 2.9 mmol) and *tert*-butylchlorodimethylsilane (217 mg, 1.4 mmol). After 8 h of stirring at room temperature, the reaction mixture was dissolved in ethyl acetate (50 mL). The solution was washed with a saturated NaCl solution (5 mLx5), and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by subjection to preparative TLC (CH_2Cl_2/MeOH/NH_4OH =200/10/1) gave **22** (357 mg, 85%): IR (neat) 3310, 1613, 1513, 1248, 1096, 1039, 836, 776 cm-1; ^1H NMR δ0.07 (s, 6H), 0.90 (s, 9H), 1.45 (bs, 1H), 2.39 (s, 3H), 2.45 (m, 1H), 2.68 (dd, 1H, *J*=9.3, 13.7 Hz), 2.74 (dd, 1H, *J*=6.4, 10.5 Hz), 2.96 (d, 1H, *J*=10.5 Hz), 3.07 (dd, 1H, *J*=4.9, 13.7 Hz), 3.79 (s, 3H), 3.85 (dd, 1H, *J*=2.4, 5.4 Hz), 4.04 (dt, 1H, *J*=2.4, 6.4 Hz), 6.85 (d, 2H, *J*=8.8 Hz), 7.17 (d, 2H, *J*=8.8 Hz); MS *m/z* (rel intensity) 350 (M^+, 0.3), 230 (100), 121 (19), 98 (17), 73 (29). HRMS calcd for $C_{19}H_{33}NO_3Si$: *m/z* 351.2230. Found: *m/z* 351.2244.

(2*R*,3*S*,4*S*)-3-Acetoxy-2-(4-methoxybenzyl)-1-methyl-4-[(*tert*-butyldimethylsilyl)oxy]-pyrrolidine (23). A mixture of **22** (493 mg, 1.4 mmol) and acetic anhydride (0.5 mL) in dry triethylamine (5 mL) was stirred at room temperature for 8 h. After evaporation of triethylamine and acetic anhydride in *vacuo*, the residue was dissolved in diethyl ether (100 mL). The ethereal solution was washed with water (10 mLx3) and a saturated NaCl solution (10 mL), and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by subjection to preparative TLC (CH_2Cl_2/MeOH=30/1) gave **23** (552 mg, 90%) as an oil: IR (neat) 1742, 1614, 1514, 1248, 1038, 835, 779 cm^{-1}; ^1H NMR δ0.06 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.89 (s, 9H, $SiC(CH_3)$), 1.82 (s, 3H, $COCH_3$), 2.37 (s, 3H, NCH_3), 2.59 (m, 1H, 2α-H), 2.67 (dd, 1H, *J*=5.4, 10.3 Hz, 5β-H), 2.75 (dd, 1H, *J*=8.8, 13.7 Hz, benzyl CH_2), 2.97 (dd, 1H, *J*=5.9, 13.7 Hz, benzyl CH_2), 3.02 (d, 1H, *J*=10.3 Hz, 5α-H; *NOE* enhancement (15.3%) was observed when a double-doublet at δ2.67 was irradiated), 3.77 (s, 3H, anisyl CH_3), 4.05 (d, 1H, *J*=5.4 Hz, 4β-H; *NOE* enhancement (9.1%) was observed when a double-doublet at δ2.67 was irradiated), 4.89 (d, 1H, *J*=3.9 Hz, 3α-H; *NOE* enhancement (4.6%) was observed when a multiplet at δ2.59 was irradiated), 6.81 (d, 2H, *J*=8.3 Hz, aromatic), 7.13 (d, 2H, *J*=8.3 Hz, aromatic); MS *m/z* (rel intensity) 394 (M^+, 0.2), 336 (8), 272 (62), 140 (5), 121 (27), 98 (100), 75 (17), 73 (18). HRMS calcd for $C_{21}H_{35}NO_4Si$: *m/z* 393.2336. Found: *m/z* 393.2316.

(+)-*N*-Methylanisomycin (1a). To a cooled (0 °C) and stirred solution of **23** (274 mg, 0.7 mmol) in THF (10 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (2.5 mL, 2.5 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for an additional 8 h . The reaction mixture was dissolved in diethyl ether (80 mL); the ethereal solution was washed with H_2O (5 mLx3) and a saturated NaCl solution (5 mL), and then dried over Na_2SO_4. Filtration and evaporation of the solvent followed by subjection of the product to preparative TLC (CH_2Cl_2/MeOH/NH_3=100/10/1) gave **1a** (146 mg, 75%). Recrystallization from hexane/ether gave a pure (+)-*N*-methylanisomycin (**1a**): mp 79-81 °C; $[\alpha]^{24}_D$ +65.1° (c=1.0, MeOH); IR (Nujol) 3078, 1742, 1612, 1514, 1248, 1029, 827 cm^{-1}; ^1H NMR δ1.83 (bs, 1H, OH), 1.87 (s, 3H, $COCH_3$), 2.37 (s, 3H, NCH_3), 2.45 (m, 1H, *J*=5.4, 5.9, 7.3 Hz, 2α-H), 2.55 (dd, 1H, *J*=5.5, 10.7 Hz, 5β-H; *NOE* enhancement (3.9%) was observed when a doublet at δ3.88 was irradiated), 2.74 (dd, 1H, *J*=7.3, 13.7 Hz, benzyl CH_2), 2.99 (dd, 1H, *J*=5.4, 13.7 Hz, benzyl CH_2), 3.78 (s, 3H, anisyl CH_3), 3.88 (d, 1H, *J*=5.4 Hz, 4β-H), 4.57 (d, 1H, *J*=5.9 Hz, 3α-H; *NOE* enhancement (4.1%) was observed when a multiplet at δ2.45 was irradiated), 6.82 (d, 2H, *J*=8.3 Hz, aromatic), 7.13 (d, 2H, *J*=8.8 Hz, aromatic); MS *m/z* (rel intensity) 279 (M^+, 0.1), 158 (64), 121 (14), 98 (100), 43 (15). HRMS calcd for $C_{15}H_{21}NO_4$: *m/z* 279.1470. Found: *m/z* 279.1494.

Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.66; H, 7.76; N, 5.05.

Acknowledgement. We gratefully acknowledge the financial support of a Grant-in-Aid for Scientific Research on Priority Areas (No. 01607001) from the Ministry of Education, Science and Culture of Japan. We thank Prof. Chihiro Kibayashi, Tokyo College of Pharmacy, for kindly providing the ^1H NMR spectra of (-)-anisomycin and related compounds. We also thank Dr. J. G. Stam, Pfizer Inc., Mr. Tadao Satoh and Mr. Masayuki Obata, Pfizer Pharmaceuticals Inc., for kindly providing a sample of (-)-anisomycin.

REFERENCES AND NOTES

1. (a) Beereboom, J. J.; Butler, K.; Pennington, F. C.; Solomons, I. A. *J. Org. Chem.* **1965**, *30*, 2334. (b) Schaefer, J. P.; Wheatley, P. F. *J. Org. Chem.* **1968**, *33*, 166. (c) Butler, K. *J. Org. Chem.* **1968**, *33*, 2136.
2. Wong, C. M. *Can. J. Chem.* **1968**, *46*, 1101.
3. Jimenez, A.; Vazquez, D. *Antibiotics*; Hahn, F. E., Ed.; Springer Verlag: Berlin, 1979; pp1-19 and references cited therein.
4. Sobin, B. A.; Tanner, F. W., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 4053.
5. Korzybski, T.; Kowszyk-Gindifer, Z.; Kurytowicz, W. *Antibiotics*; American Society of Microbiolgy: Washington, DC., 1978; Vol. 1, pp343-346.
6. (a) Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1969**, *17*, 1405. (b) Schumacher, D. P.; Hall, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 6076.
7. (a) Wong, C. M.; Buccini, J.; Chang, I.; Raa, J. T.; Schwenk, R. *Can. J. Chem.* **1969**, *47*, 2421. (b) Felner, I.; Schenker, K. *Helv. Chim. Acta.* **1970**, *53*, 754. (c) Verheyden, J. P. H.; Richardson, A. C.; Bhatt, R. S.; Grant, B. D.; Fitch, W. L.; Mofatt, J. G. *Pure Appl. Chem.* **1978**, *50*, 1363. (d) Buchanan, J. G.; MacLean, K. A.; Wighyman, R. H.; Paulsen, H. Wighyman, R. H. *J. Chem. Soc., Perkin Trans. I* **1985**, 1463. (e) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 1069. (f) Shono, T; Kise, N. *Chem. Lett.* **1987**, 697. (g) Baer, H. H.; Zamkanei, M. *J. Org. Chem.* **1988**, *53*, 4786. (h) Jegham, S.; Das, B. C. *Tetrahedron Lett.* **1988**, *29*, 4419. (i) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 1861. (j) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240.
8. Meyers, A. I.; Dupre, B. *Heterocycles* **1987**, *25*, 113.
9. (a) Tokuda, M.; Yamada, Y.; Takagi, T.; Suginome, H.; Furusaki, A. *Tetrahedron Lett.* **1985**, *26*, 6085. (b) Tokuda, M.; Yamada, Y.; Takagi, T.; Suginome, H.; Furusaki, A. *Tetrahedron* **1987**, *43*, 281.
10. Tokuda, M.; Miyamoto, T.; Fujita, H.; Suginome, H. *Tetrahedron* **1991**, *47*, 747.
11. Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1985**, *26*, 3255; Khanov, M. T.; Sultanov, M. B.; Egorova, T. A. *Farmakol. Alkaloidov Serdech. Glikoyidov.* **1971**, 210 [*C.A.*, **1972**, *77*, 135091r].
12. The yields in the Wittig reaction of **5** or **10** to give **6** or **11** were not optimized.
13. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Amer. Chem. Soc.* **1971**, *93*, 2897.
14. More experiments must be carried out before a firm explanation can be made of the stereochemistry of the cyclization. However, the absorption of the nitrogen atom and the double bond of **12a** on the anode surface followed by one-electron oxidation and a subsequent cyclization would result in a preferential formation of one of possible stereoisomers.
15. Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett.* **1992**, *33*, 6359.